carcinoma of the ovary, which affects younger women. While 60-80% of advanced ovarian cancers will initially respond to cisplatin-based chemotherapy, the majority will relapse and acquire a phenotype that renders them resistant to a broad range of drugs. From a 23 year old patient, small cell carcinoma tissue of the ovary was resected during unilateral adnexectomy, and by the method of collagenase cells were isolated and cultured. These epithelial ovarian tumour cells were found by PCR to express high levels of MRP and p53 genes. The multi-drug resistance-associated protein plays a significant role in the multi-drug resistance phenotype of ovarian tumour cells. Furthermore, p53 overexpression is associated with p53 mutations contributing to the dysfunction of this phosphoprotein such as inhibition of apoptosis after chemotherapy. To circumvent both of these mechanisms of drug resistance, we entrap cisplatin inside the bilayers of liposomes consisting of 3ß[N-(N', N'-dimethylaminoethane) carbomoyl], cholesterol and helper lipid dioleyol phosphatidyl-ethanolamine, which have been found onto molecules of p53 gene. Entrapped cisplatin is protected by binding to plasma proteins and HLD attack. With this approach, cisplatin molecules should overcome MRP efflux, and transfection of p53 could resensitize these cells, including apoptosis. After incubating these tumour cells with the liposomal carriers, we observe under electron microscopy a novel mechanism of endocytosis via caveolae, leading to the fusion of liposomes with the nuclear envelopes of the tumour cells. At this point intranuclear restoration of wild type p53 occurs and cisplatin molecules interact with nucleophilic sites on DNA, RNA and protein forming bifunctional, intrastrand and cross-links and DNA conformation resulting in inhibition of DNA synthesis and apoptosis. Control samples consisting of free wt-p53 and cisplatin incubating with tumour cells have not exhibited extensive cellular alterations, implying no cellular entry of these substances. Transmission and scanning electron microscopy has showed apoptotic changes such as membrane blebbing, chromatin aggregation at the nuclear membrane, cellular condensation, formation of membrane bound vesicles such as apoptotic bodies leading to secondary necrosis of the tumour cells treated with liposomes. These results were correlated with cytotoxity assays such as measurements of metabolic activity by tetrazolium salt MTT assay, exhibiting reduced metabolic activity and measurement of DNA synthesis by the thymidine analogue 5-bromo-2 deosyuridine (BrdU) exhibiting reduced DNA synthesis, implying enhanced chemosensitivity and induction of apoptosis compared to tumour cells treated with free wt p53 and cisplatin. Furthermore, measurement of apoptotic frequency by TUNEL (TdT mediated dUTP-biotin nick end labeling) exhibited higher apoptotic frequency after liposomal treatment. Finally, flow cytometric analysis of the tumour cells after liposomal treatment has showed cell arrest in G1 phase, while the cells of the control samples progressed through the cell cycle. Thus, we can observe cytotoxic synergy of chemotherapy and gene therapy against ovarian carcinoma by circumventing their drug resistance phenotype.

[155] Prognostic value of serial CA 125 measurements during chemotherapy for patients with advanced ovarian cancer

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Aim: Serum CA 125 concentrations measured before and during chemotherapy may provide additional information for prognostic assessment of patients with epithelial ovarian cancer (EOC), and enable discrimination between patients who are likely to benefit from further therapy and those who will not.

Materials and methods: Medical records of 40 patients with advanced EOC, treated at the Department of Obstetrics and Gynaecology of the University Hospital Nijmegen Between July 1984 and April 1993, were examined. All patients had primary cytoreductive surgery followed by platinum-based chemotherapy. Serum samples were obtained before surgery and during chemotherapy. Follow-up information and patient and tumor characteristics were abstracted from medical records until December 1, 1994. By using multivariate Cox proportional hazards models for disease-free and overall survival it was evaluated whether outcome prediction was improved by inclusion of serum CA 125 quantitations.

Results: Only FIGO stage and extent of residual tumor were significant independent prognostic factors before the start of chemotherapy. When such regression models were constructed after subsequent courses of chemotherapy, serum CA 125 measurements conducted after each of the first three chemotherapy courses improved the prediction of disease-free survival. Prediction of overall survival was improved by inclusion of serum CA 125 measurements after courses 1-6.

Conclusion: Inclusion of serum CA 125 measurements during chemotherapy improved prognostic assessment of patients with advanced ovarian cancer.

[156] Tissue polypeptide specific antigen (TPS) as a complementary test of CA 125 in ovarian cancer

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This study was carried out to test the utility of TPS in ovarian cancer. We also intended to evaluate its additional information about cell proliferative activity in ovarian tumoral process.

The study included 63 cases of ovarian pathology (36 malignant and 27 benign).

The histological and staging composition of malignant group was: 32 epithelial and 4 non-epithelial. FIGO - classification: I = 9 cases; II = 8; III = 15; IV = 4.